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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,235	08/27/2001	Girish Sahni	07064-009002	5356

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EXAMINER
SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
1652	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,235	SAHNI ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *4-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 32* is/are rejected.

7)☒ Claim(s) *2 and 3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group II, Claims 1-3, 9, and 32 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the fact that the DNA of Group I has uses other than the manufacture of the protein of Group II does not by itself justify the restriction and, further, that the wording of Claim 4 references Claim 1 and it would be appropriate to examine both groups. This is not found persuasive. Restriction practice is not governed by the dependent relationship of claims. 35 U.S.C. 121 allows restriction of inventions which are independent or distinct. The reasons Groups I and II are distinct are described in the prior action. Groups I and II do not have the same classification and would, therefore, require separate searches; said multiple searches would be a burden on the Office. The restriction requirement is still deemed proper and is therefore made FINAL.

We thank the applicants for pointing out that Claim 9 belongs in Group III, not Group I. Claims 4-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected Inventions, there being no allowable generic or linking claim. Claims 1-3 and 32 are hereby examined.

Specification-Objections

Title

The title is objected to for using the word "novel" which, is redundant in the title of a patent.

Abstract

The abstract of the disclosure is objected to because (i) the first sentence is not a complete sentence and (ii) it does not adequately reflect the invention of this application. Description of the recited hybrid streptokinase/fibrin binding-domain plasminogen activator should be included. Correction is required. See MPEP § 608.01(b).

Figure Legends

The figure legends are objected to for the following reasons.

Fig 4: The identity of the streptokinase polynucleotide, from which the restriction map of Fig 4 is derived, should be stated.

Fig 7: The identity of the streptokinase polynucleotide, from which the restriction map of Fig 7 is derived, should be stated.

Fig 24: The five time curves displayed should be identified; do they represent different proteins, different concentrations of a single protein, or some other differing parameter?

Appropriate corrections are required.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claims-Objections

Claim 2 is objected to due to poor grammar and spelling for the following reasons. There should be a comma after wherein. Bind in line two should be bound. There should be a comma after selected and after thereof in order to set off the phrase ", selected from the pair of fibrin binding domains 4 and 5, domains 1 and 2, or modifications thereof, ". The word pari on line two should be corrected to pair.

Claim 3 is objected to for lacking a period (.) at the end.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "pronounced" (line 8) in Claim 1 is a relative term which, renders the claim indefinite. The term "pronounced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In addition, the terms "suitable parts" (line 2), "various motifs" (line 5), and "suitable" (line 9) are vague and indefinite. The terms "suitable parts", "various motifs", and "suitable" are not defined by the claim, the specification does not provide a definition, and one of ordinary skill in the art would not be reasonably apprised of the subject matter which applicant regards as the invention. Therefore, Claim 1 and Claims 2 and 3, as dependent on Claim 1, are rejected under 35 U.S.C. 112, second paragraph.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The fibrin binding domains 1, 2, 4, and 5 have not been distinctly define ie by disclosing the specific sequences for said domains. One of ordinary skill in the art would not be reasonably apprised of the metes and bounds of domains encompassed by the invention. Therefore, Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. The phrase "etc." renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "etc"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 32 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for the hybrid plasminogen activator comprising fusion of streptokinase with fibrin binding-domain proteins as encoded by the sequences set forth in Figs 17b, 19b, 21b, and 22b. However, the specification does not reasonably provide enablement for any hybrid plasminogen activator comprising any streptokinase and any pair of fibrin binding-domains derived from human fibronectin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 2 are so broad as to encompass any hybrid plasminogen activator comprising any streptokinase and any pair of fibrin binding-domains, 4 and 5 or 1 and 2, derived from human fibronectin wherein, plasminogen activation occurs after a lag. Claim 3 is so broad as to encompass any plasminogen activator comprising any streptokinase and any pair of fibrin binding-domains, 4 and 5 or 1 and 2, derived from human fibronectin wherein, plasminogen activation occurs after a lag of 5-30 mins. Claim 32 is so broad as to encompass any hybrid

plasminogen activator. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of plasminogen activators broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired plasminogen activation and fibrin binding requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the plasminogen activators encoded by the sequences set forth in Figs 17b, 19b, 21b, and 22b.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1 and 2 which encompass any hybrid plasminogen activator comprising any streptokinase and any pair of fibrin binding-domains, 4 and 5 or 1 and 2, derived from human fibronectin wherein, plasminogen activation occurs after a lag. The specification does not support the broad scope of Claim 3 which encompasses any plasminogen activator comprising any streptokinase and any pair of fibrin

binding-domains, 4 and 5 or 1 and 2, derived from human fibronectin wherein, plasminogen activation occurs after a lag of 5-30 mins. The specification does not support the broad scope of Claim 32 which encompasses any hybrid plasminogen activator. The specification does not support the broad scope of Claims 1-3 or 32 because the specification does not establish: (A) regions of the proteins' structure which may be modified without effecting the plasminogen activation or fibrin binding; (B) the general tolerance of the plasminogen activation and fibrin binding to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of hybrid plasminogen activators with an enormous number of amino acid modifications of the plasminogen activators encoded by the polynucleotide set forth in Figs 17b, 19b, 21b, and 22b. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-3 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of hybrid plasminogen activator proteins. The specification teaches the structure of only four representative species of such proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a hybrid plasminogen activator. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by Malke, 1993 (IDS). Malke teaches hybrid plasminogen activators comprised of streptokinase fused to either the fibrin binding-domains derived from human plasminogen (page 3, lines 5-13) or a kringle domain (page 9, lines 23-25). These fusion proteins are stabilized in phosphate-buffered saline during purification. Therefore, Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by Malke, 1993.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al, 1992 in view of Malke, 1990 (IDS) and further in view of Atkinson et al, 1998. Brown et al, teach the preparation of a protein comprised of the N- or C-terminal fibrin binding domains of fibronectin cross-linked to streptokinase (col 17, section E). Said protein of Brown et al contains 38-52% activity compared to unconjugated streptokinase (Table 6). Brown et al do not teach a protein whereby fibrin binding-domains of fibronectin are fused to streptokinase via a peptide bond. Malke, 1990 teach the preparation of fusion proteins using molecular DNA techniques wherein, a fibrin binding domain derived from human plasminogen is fused to streptokinase (page 3, lines 10-13). Since preparation of fusion proteins is common in the art, it would have been obvious to a person of ordinary skill in the art to use the method of Malke to prepare a fusion protein derived from the fibrin binding-domains of fibrinogen and the streptokinase used by Brown et al. Motivation to do so is provided by the desire to produce a product that is an improvement on the product of Brown et al using an easier method. The expectation of success is high as preparation of fusion proteins is standard technology. Although not demonstrated by Brown et al, the characteristic of carrying out plasminogen activation only after a lag period of 5-30 mins, as recited in Claim 3, would be inherent to a fusion protein prepared from the components used to make their cross-linked protein. This inherency is further

supported by the fact that the cross-lined protein of Brown et al has 38-52% of the activity compared to unconjugated streptokinase (Table 6). Preparation of pharmaceutical compositions comprising enzymes and stabilizers is common in the art (Atkinson et al,) and one would also be motivated to make such a composition for delivery of a fusion protein, made based on the teachings of Brown et al and Malke, to a patient. Therefore, Claims 1-3 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al, 1992 in view of Malke, 1990 and further in view of Atkinson et al, 1998.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.

Rebecca Prouty

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600